Genzyme
Regulatory Affairs

One Kendall Square
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October 27, 1999

Dockets Management Branch,
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 99D-2873

Dear Sir or Madam:

Genzyme Corporation hereby submits its written comments on the draft guidance entitled "Guidance for Industry and FDA Reviewers on Evidence Models for the Least Burdensome Means to Market". Genzyme appreciates the opportunity to comment on this long awaited and important document. Genzyme is a leading manufacturer of pharmaceuticals, biologics, devices and *in vitro* diagnostic products (IVD's).

First, Genzyme is greatly disappointed that this draft guidance excluded *in vitro* diagnostic products. Clearly, the FDA Modernization Act of 1997 (FDAMA) did not intend to exclude them from the least burdensome appropriate means of evaluating device effectiveness. Genzyme believes the principles are similar enough that the draft guidance can and should include IVD's.

Also disappointing, was the process in which this draft guidance was developed. No dialogue was allowed with the stakeholders until the draft guidance was issued. The result is that the document proposed is 180 degrees opposed to the industry's position and what we believe to be the congressional intent of the legislation.

According to this document, the default position is a randomized, controlled, prospective study. FDA then sets up a series of contingency questions that must be answered to avoid the default position. FDA maintains that any alternate that is less burdensome should be justified according to this model. According to the industry model proposed by HIMA, FDA must justify the requirements that place additional burden on companies as described in their hierarchical table. In the HIMA model FDA must have an explicit unanswered question to go up to the next level of burden. HIMA's proposal is a "bottoms up" scheme and FDA's is a "top down". Intuitively, a bottoms up scheme is less burdensome than starting at the most burdensome and working down.

In order to achieve the stated goal of "...a process model for reaching a decision about the need for clinical data and the type of clinical data that is the least burdensome means to support successful pre-market review", consideration should be given of the following:

- Utilize the Pre-IDE meeting or pre-Notification meeting by starting with no *preconceived* expectations.
- Consider the appropriate application of risk vs. benefit.
- Proportion the level of proof to the possible risk. No medical intervention (device, drug or biologic) is totally safe. All involve risk. The law only requires "reasonable assurance" of safety and efficacy.

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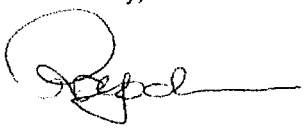
- Consider "accepted medical practice" in approval decisions. Much of accepted clinical practice has been derived without evidence based outcomes studies.

- Review and update the clinical utility memorandum in light of the least burdensome requirements. Evidenced based, clinical outcomes studies should not be the default position. Remember, 21CFR 860.7(e)(1) requires only clinically significant results. A new medical intervention is excessively burdened by proof of change in patient outcome beyond the level of clinical significance required for establishing the *efficacy of the product consistent with the stated labeling.* Many products are simply tools to aid the caregiver. Each of these tools may not necessarily have to change patient outcome. The tools may not even benefit the patient further than present tools at all –only provide benefit to the user (physician). The public health can also benefit by many small advances to patients or caregivers. There have been times (because of the clinical utility memorandum) when products have been overburdened in their requirements to prove changes in clinical practice or patient outcomes.

- Consider using surrogate endpoints more often than just in long longitudinal trials or in long term follow-up. Although mentioned in this draft guidance, we believe insufficient emphasis has been placed on this point. Surrogate end points and surrogate populations offer tremendous benefit in providing less burdensome approaches to clinical studies.

Genzyme is pleased that the agency has decided to engage industry from this point forward in further developing this draft guidance. We further believe that this guidance should set out philosophical guidance for stakeholders to consider in product or technology specific guidance documents. The technology specific documents should be jointly developed by the agency, industry and the medical community. We would be pleased to join with FDA in this pursuit.

Sincerely,



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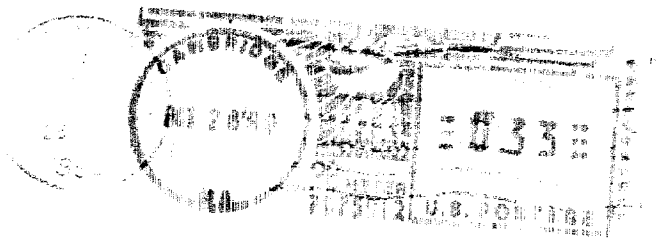

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